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Designation: E2968 – 23

Standard Guide for Application of Continuous Manufacturing (CM) in the Pharmaceutical Industry[1]

This standard is issued under the fixed designation E2968; the number immediately following the designation indicates the year of original adoption or, in the case of revision, the year of last revision. A number in parentheses indicates the year of last reapproval. A superscript epsilon (ε) indicates an editorial change since the last revision or reapproval.

1. Scope

1.1 This guide introduces key concepts and principles to assist in the appropriate selection, development and operation of CM technologies for the manufacture of pharmaceutical products. Athough selected concepts covered here can be applied to biopharmaceutical CM (BioCM), the focus of this guide is on non-biopharmaceutical applications.

1.2 Particular consideration is given to the development and application of the appropriate scientific understanding and engineering principles that differentiate CM from traditional batch manufacturing.

1.3 Most of the underlying concepts and principles (for example, process dynamics and process control) outlined in this guide can be applied to both Drug Substance (DS) and Drug Product (DP) processes. However, it should be recognized that in Drug Substance production the emphasis may be more on chemical behavior and dynamics in a fluid phase whereas for solid drug product manufacture there may be a greater emphasis on the physical behavior and dynamics in a solid/powder format.

1.4 This guide is also intended to apply in both the development of new processes, or the redesign of existing ones.

1.5 All values are stated in SI units. No other units of measurement are included in this standard.

1.6 *This standard does not purport to address all of the safety concerns, if any, associated with its use. It is the responsibility of the user of this standard to establish appropriate safety, health, and environmental practices and determine the applicability of regulatory limitations prior to use.*

1.7 *This international standard was developed in accordance with internationally recognized principles on standardization established in the Decision on Principles for the Development of International Standards, Guides and Recommendations issued by the World Trade Organization Technical Barriers to Trade (TBT) Committee.*

2. Referenced Documents

2.1 *ASTM Standards:*[2]

E2363 Terminology Relating to Manufacturing of Pharmaceutical and Biopharmaceutical Products in the Pharmaceutical and Biopharmaceutical Industry

E2475 Guide for Process Understanding Related to Pharmaceutical Manufacture and Control

E2537 Guide for Application of Continuous Process Verification to Pharmaceutical and Biopharmaceutical Manufacturing

E2629 Guide for Verification of Process Analytical Technology (PAT) Enabled Control Systems

E2898 Guide for Risk-Based Validation of Analytical Methods for PAT Applications

2.2 *Regulatory Guidance and Other Documents:*

21 CFR 210.3 Current Good Manufacturing Practice in Manufacturing, Processing, Packing or Holding of Drugs, General Definitions[3]

EMA Guideline on process validation for finished products information and data to be provided in regulatory submissions

EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use, Annex 15: Qualification and Validation

FDA Guidance for Industry PAT A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance (2004)[3]

FDA Guidance for Industry Process Validation: General Principles and Practices (2011)[3]

ICH Harmonized Tripartite Guideline, Continuous Manufacturing of Drug Substances and Drug Products, Q13 (Step 2b version, dated 29 July 2021)[4]

ICH Harmonized Tripartite Guideline, Pharmaceutical

[1] This guide is under the jurisdiction of ASTM Committee E55 on Manufacture of Pharmaceutical and Biopharmaceutical Products and is the direct responsibility of Subcommittee E55.11 on Process Design.

Current edition approved Jan. 1, 2023. Published February 2023. Originally approved in 2014. Last previous edition approved in 2014 as E2968 – 14. DOI: 10.1520/E2968-23.

[2] For referenced ASTM standards, visit the ASTM website, www.astm.org, or contact ASTM Customer Service at service@astm.org. For *Annual Book of ASTM Standards* volume information, refer to the standard's Document Summary page on the ASTM website.

[3] Available from Food and Drug Administration (FDA), 10903 New Hampshire Ave., Silver Spring, MD 20993-0002, http://www.fda.gov.

[4] Available from International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), ICH Secretariat, Route de Pré-Bois, 20, P.O Box 1894, 1215 Geneva, Switzerland, https://www.ich.org.

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Quality System, Q10 (Step 4 version, dated 4 June 2008)[4]

3. Terminology

3.1 *Definitions:*

3.1.1 For general definitions, refer to Terminology E2363 and Guides E2537 and E2475.

3.2 *Definitions of Terms Specific to This Standard:*

3.2.1 *back mixed process*—a process with a residence time distribution (RTD) that is significant compared to the mean residence time. A process where the deviation of a material's residence time distribution from its mean residence time is large enough to indicate significant mixing of materials introduced at a single point into the process at different times.

3.2.1.1 *Discussion*—For example, in a fully back mixed process, quantities of material will be mixed into a single homogeneous condition such that a rapid step change in the properties of inlet material will not result in an equivalent step change in the properties of the output material but will be reflected in a more gradual change. The rate of this change will depend on the material properties, equipment characteristics, residence volume, and the residence time distribution/degree of mixing. A fully back mixed process may be considered and modeled as one or more continuously stirred tank reactors (CSTR) connected in series.

3.2.2 *continuous manufacturing (CM)*——a process where, during normal operation, raw materials are continuously fed into the system at the same time as product is continuously removed from the system. In the context of this guide, continuous manufacturing is considered to be a series of 2 or more continuous, or quasi continuous, transformation steps or unit operations which are integrated into a CM line which may be part of a complete CM plant.

3.2.2.1 *Discussion*—The term continuous process may be used to refer to a single continuous process step or unit operation where the output may not be a finished product. A single continuous process step or unit operation is not considered to be representative of CM as considered by this guide as continuous processes are often used as unit operations within batch (or bin to bin) production.

(1) In a CM process, the degree of transformation of any specific quantity of material from an initial condition into the subsequent condition is a function of the process parameters applied and either:

(a) The position of the material as it flows through the process,

(b) The duration that the material has been within the process, or

(c) A combination of both (a) and (b).

(2) A CM process transforms a pre-defined quantity of material into a pre-defined physical quantity of product which is then subjected to a disposition decision. The amount of expected final product produced is predefined by the amount of starting material but can be divided into separate lots in a flexible way based on principles of science and risk.

(3) Alternatively, CM may be operated with a 'flexible' run-time, in which quantities of product are defined during the operation of the process in a flexible way, based on principles of science and risk (for example, as any entity produced in a certain time, or containing a certain lot of a starting material), and subjected to a disposition decision.

(4) A process consisting of a series of interconnected unit operations or transformations can be considered to be continuous even if it contains transformations of defined quantities of material which might be considered to be composed of a sequence of individual discrete events.

(5) During periods of startup, shutdown or processing of small quantities of material, or both (for example, for development/experimental or clinical studies), it is possible that not all unit operations within a continuous production line will be in normal or steady state conditions at the same time. For example: the first unit operation could already be shut down while the material is processed further in subsequent unit operations. This condition should not automatically invalidate the definition of the process as representative of normal continuous operation; however, care must be taken to understand the impact of this mode of operation on product quality.

3.2.3 *critical process parameter (CPP)*—a process parameter whose variability has a significant impact on a CQA and therefore should be monitored or controlled to ensure the process produces the desired quality (ICH Q8 (R2)).

3.2.4 *critical quality attribute (CQA)*—a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality (ICH Q8 (R2)).

3.2.5 *dynamic or adaptive process control system*—an automated control system that utilizes process and control models and the use of dynamic critical process parameters (CPP) (see Guide E2629 - 11, section 4.2 for detail description) to deliver required product quality. Depending on the dynamics of the process the corrections may be applied immediately as a step change or as a time dependent function (for example, a ramp or exponential function). Such real time control systems may include, for example:

3.2.6 *feedback control*—a control strategy which is intended to eliminate drift or deviation in a specific product attribute away from the target (setpoint) by means of:

(1) Measuring the attributes of material leaving a process operation,

(2) Comparing the measured values with target (setpoint) values for the attributes, and

(3) Using a process model or real-time tuning (that is, reaction to action) in order to calculate revised setpoint values for the relevant process conditions.

3.2.7 *feed forward control*—a control strategy which measures either: (*1*) specific critical attributes of materials as they enter a specific process, or (*2*) other upstream factors (for example, flow rates, temperature, etc.), and uses this information in combination with an appropriate process model to adjust the setpoint of the process conditions in order to reduce the impact of the upstream change on the quality of the material leaving the process step.

3.2.8 *multivariate model based control*—measurements of one or more product attributes and process conditions are used in a model of the process to determine the process conditions required to achieve the desired product quality.